THE EFFECT OF FLUPHENAZINE ON STEADY STATE PLASMA LEVELS OF NORTRIPTYLINE

Biochemical studies (Sjöqvist, Alexanderson, Asberg, Bertilsson, Borga, Hamberger & Tuck, 1971; Gram & Overø, 1973) have shown that the metabolic degradation of tricyclic antidepressant compounds, particularly nortriptyline, is delayed by the concomitant administration of certain phenothiazine tranquilizers. This causes an elevation of the steady state plasma tricyclic antidepressant level and further work has been done on the relationship of psychiatric symptoms to plasma tricyclic antidepressant levels in depressed patients.

Results have been somewhat conflicting. Braithwaite, Goulding, Theano, Bailey & Coppen (1972) found almost linear positive relationship between tricyclic antidepressant level and clinical improvement; Asberg, Crønholm, Sjöqvist & Tuck (1971) proposed an optimal range of tricyclic antidepressant plasma level corresponding to clinical improvement; Kragh-Sørensen, Asberg & Eggert-Hansen (1973) suggested an upper limit of nortriptyline level beyond which therapeutic effect falls off; and Burrows, Davies & Scoggins (1972) failed to find any relationship between tricyclic antidepressant levels and therapeutic effect. Glassman, Hurwic & Perel (1973) suggested that these discrepancies might be due to failure of these studies to allow for variation in protein binding of the drugs, and showed a large inter-individual variation of protein binding in patients treated with imipramine.

A product which has been widely used for the treatment of mixed states of anxiety and depression contains fluphenazine (0.5 mg) with nortriptyline (10 mg) per tablet ('Motival'), and much published work attests to its effectiveness (Anderson, Lambert & Pigott, 1972; Grozier, 1972; Pigott, 1972). This study has been undertaken to assess whether the phenothiazine has any effect on the plasma level of nortriptyline in patients treated with this combination.

A crossover design was used, nine female patients ages 31-71 being randomly allocated to either nortriptyline (10 mg) q.d.s. first, or fluphenazine with nortriptyline tabs. 1 q.d.s. first. Six patients were given a 3-week course of fluphenazine with nortriptyline first followed by 3 weeks nortriptyline, and three patients *vice versa*. Patients included were free of hepatic or renal disease and were selected on the basis that they would not require any of the following drugs during the course of the study: barbiturates, glutethimide, phenylbutazone, diphenylhydantoin,

dichloralphenazone, Mandrax, other phenothiazines or tricyclic antidepressants.

Plasma nortriptyline levels were estimated twice weekly by the tritiated acetic anhydride method of Hammer & Brodier (1967) and the steady state nortriptyline levels compared for each patient during the two treatment regimes using a two sample *t* test. Only values obtained during the last 2 weeks of each treatment period were included in the analysis, which is summarized in Table 1.

As can be seen, only one patient showed a significant difference in steady state nortriptyline level between nortriptyline only and fluphenazine with nortriptyline treatment periods. This contrasts with the very great inter-individual range of steady state nortriptyline levels (11.17-115.03 ng/ml for nortriptyline only, 11.35-97.73 for fluphenazine with nortriptyline), which is in keeping with previous studies (Sjöqvist *et al.*, 1971). Two patients (4 and 8) were taking oral contraceptive steroids, but their plasma levels are within the range of that of the remaining patients.

Examination of the nortriptyline plasma values found, makes drug defaulting unlikely to have occurred to any significant extent, and it seems probable that the intra-individual stability of steady state nortriptyline level is due to the low dose of fluphenazine involved, although the possibility that fluphenazine behaves differently in this respect to perphenazine and chlorpromazine (Gram & Overø, 1972) has not been disproved.

Alexanderson, Evans & Sjöqvist (1969), as a result of an intra-pair study on monozygotic twins, stressed the importance of concomitant drug exposure in determining steady state plasma levels of nortriptyline. Gram & Overø (1972) studied five patients before and during treatment with perphenazine (20-48 mg/day) and found a 10-30% elevation of peak nortriptyline plasma levels following a single dose of [¹⁴C]-nortriptyline (50 mg) during the period of concomitant perphenazine therapy. The present work appears to be the first within-subject study to examine the possible effect of a phenothiazine on steady state plasma levels of a tricyclic antidepressant, and has shown that a therapeutic dose of fluphenazine is apparently not high enough to interfere with the metabolism of nortriptyline.

It is interesting to note that, irrespective of preparation used, the mean steady state plasma level of nortriptyline was slightly lower in each of the nine patients during the second period of

Table 1 Two-sample *t*-test between drugs on mean steady state plasma levels for each patient

Patient number	Mean steady state plasma nortriptyline level (n = 4) (ng/ml)		Nortriptyline alone	<i>t</i> value	<i>d.f.</i>	Significance
	Dose nortriptyline (mg kg ⁻¹ day ⁻¹)	Fluphenazine + nortriptyline				
1	0.60	27.55*	22.62	+2.27	6	NS
2	0.76	115.03*	97.73	+1.32	6	NS
3	0.73	11.35*	10.47	+0.69	6	NS
4	0.60	11.17	11.35*	-0.11	6	NS
5	0.57	39.58*	30.84	+5.70	6	<i>P</i> = 0.01
6	0.62	15.07	18.69*	-1.90	6	NS
7	0.53	50.05*	48.55	+0.68	6	NS
8	0.74	26.13	27.22*	-0.50	6	NS
9	0.52	15.95*	13.87	+1.62	6	NS

* Indicates drug taken first
NS, not significant

treatment (mean percentage decrease $\pm$ s.d. 11.53 ± 7.67 ; $P < 0.002$). O'Malley, Browning, Stevenson & Turnbull (1973), have previously reported tricyclic antidepressant compounds to be weak inducers of drug metabolism in man, and it is conceivable that this slight reduction in steady state nortriptyline level could have resulted from an induction effect brought about during the course of the tricyclic antidepressant therapy.

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